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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,883	05/14/2001	Lex M. Cowsert	ISPH-0576	9012

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EXAMINER
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ART UNIT	PAPER NUMBER
1635	10

DATE MAILED: 11/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/854,883	Cowsert et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sept. 18, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, and 4-44* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, and 4-44* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 2, 4-44 are pending in the instant application.

Election/Restriction

Applicant's election without traverse of SEQ ID No: 243 in Paper No.9 is acknowledged.

Applicant's election of SEQ ID NO: 243 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,261,840. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims of USPN 6,261,840 are drawn to compositions comprising specific antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of PTP1B in vitro, and which antisense oligonucleotides optionally comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-methyl cytosine modified nucleobases, or are chimeric oligonucleotides and which compositions further comprise colloidal dispersion systems and pharmaceutically acceptable carriers, and the instant pending claims are drawn to compositions comprising antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of PTP1B in vitro, and which antisense oligonucleotides optionally comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-methyl cytosine modified nucleobases, or are chimeric oligonucleotides and which compositions further comprise colloidal dispersion systems and pharmaceutically acceptable carriers.

Claims 29-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 56-131 of copending Application No. 09/629,644. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed claims of US application 09/629,644 are drawn to methods of decreasing blood glucose levels in an animal, including human and rodent, comprising the administration of antisense oligonucleotides to an appropriate target cell including adipose, kidney and liver cells, which specifically target and inhibit the expression of PTP1B, and which antisense oligonucleotides optionally comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-methyl cytosine modified nucleobases, or are chimeric oligonucleotides, and the pending claims of the instant application are drawn to methods of decreasing blood glucose levels in an animal, including human and rodent, comprising the administration of antisense oligonucleotides between 8-50 nucleobases to an appropriate target cell including adipose, kidney and liver cells, which specifically target and inhibit the expression of PTP1B, and which antisense oligonucleotides optionally comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-methyl cytosine modified nucleobases, or are chimeric oligonucleotides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 14, line 2, the term " active site" is vague and unclear. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-28, 33-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro and in vivo inhibition of mouse PTP1B comprising the intraperitoneal injection of SEQ ID NO: 166 in the mouse Type 2 diabetes model (db/db), which sequence is an antisense oligonucleotide which targets the coding region of PTP1B, and whereby blood and plasma glucose levels were decreased in this Type 2 diabetes model upon inhibition of PTP1B expression, and further whereby body weight gain was comparable to wild type body weight gain upon inhibition of PTP1B expression in treated db/db

mice, does not reasonably provide enablement for the treatment of any disease or condition which is suspected of being associated with PTP1B in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of treating or preventing any disease or condition in an organism which is suspected of being associated with, or is associated with PTP1B, which diseases or conditions include any metabolic or hyperproliferative condition.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success

of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating, preventing or delaying the onset of any and/or all conditions or diseases suspected of being associated with PTP1B comprising the administration of antisense oligonucleotides which specifically target and inhibit the expression of PTP1B. The specification teaches the inhibition of PTP1B expression in vitro in various target cell lines and in a Type 2 diabetes mouse model (db/db) comprising the intraperitoneal administration of SEQ ID NO: 166, which targets the coding region of PTP1B, whereby blood and plasma glucose levels were decreased in this Type 2 diabetes model upon inhibition of PTP1B expression, and further whereby body weight gain was comparable to wild type body weight gain upon inhibition of PTP1B expression in treated db/db mice. The specification fails to teach the treatment or prevention of any and/or all conditions or diseases which are suspected of being associated with PTP1B. One skilled in the art would not accept on its face the examples given in the specification of the inhibition of PTP1B expression in vitro and in vivo as being correlative or representative of the successful treatment or prevention of any and/or all conditions or diseases suspected of being associated with PTP1B expression in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of

antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed, which treatment methods are for any and/or all conditions or diseases suspected of being associated with PTP1B.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods of treating, preventing or delaying the onset of any disease or condition in an organism which is suspected of being associated with, or is associated with PTP1B, which diseases or conditions include any metabolic or hyperproliferative condition, comprising the administration of antisense oligonucleotides which specifically target and inhibit the expression of PTP1B. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring PTP1B, such that all PTP1B expression is inhibited appropriately *in vivo,* and further that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with PTP1B in an organism. Since the specification fails to provide any particular guidance for the successful treatment or prevention of any and/or all diseases or conditions associated, or suspected of being associated with PTP1B in an organism, and since determination of these factors for a particular target gene in an organism

is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by either Huang et al. or Olefsky.

Huang et al teach antisense oligonucleotides between 8-30 nucleobases which inhibit the expression of PTP1B in target cells in vitro (See entire abstract).

Olefsky teaches antisense oligonucleotides between 8-30 nucleobases which inhibit the expression of PTP1B in target cells in vitro (abstract; column 5, lines 23-65).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Huang et al or Olefsky as applied to claims 1 and 2 above, in combination with Chernoff et al, further in view of Milner et al and Baracchini et al.

Huang et al and Olefsky are relied upon as cited in the 102 rejection above.

Chernoff et al teach the nucleotide sequences encoding PTP1B (abstract, page 2735 and figure 2, page 2737).

The primary references of Huang et al, Olefsky and Chernoff et al do not teach antisense oligonucleotides which target PTP1B and further comprise internucleoside, sugar or nucleobase modifications, nor chimeric antisense molecules.

Milner et al teach the screening of antisense oligonucleotides for their ability to inhibit a target gene of known sequence (See entire text, especially).

Baracchini et al teach chimeric antisense as well as phosphorothioate internucleoside, 2'-O-methoxyethyl sugar, 5-methyl cytosine nucleobase modifications and chimeric antisense oligonucleotides (See especially column 6, line 18-column 8, line 56).

It would have been obvious to one of ordinary skill to design and use antisense molecules for the specific inhibition of PTP1B expression, since the sequence for PTP1B was taught previously by Chernoff *et al* and antisense inhibition of PTP1B was taught previously by both Huang et al and Olefsky. One of ordinary skill in the art would have been motivated to inhibit PTP1B because it had been taught previously by Olefsky that aberrant expression of PTP1B was associated with some forms of diabetes and cellular hyperproliferation. One of ordinary skill in the art would have expected that antisense molecules targeting translated and untranslated regions of the PTP1B gene would inhibit PTP1B expression, and the methods for screening such antisense molecules had been taught previously by Milner *et al.* and James. One of ordinary skill in the art would have been motivated to incorporate internucleotide, sugar and nucleobase modifications into such antisense molecules because it had been taught previously by Baracchini *et al.* that such modifications enhance antisense stability and cellular uptake. One of ordinary skill in the art would have expected that the incorporation of such modifications into antisense molecules would render them less accessible to nuclease degradation, because this had been taught previously by Baracchini *et al.*

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

November 4, 2002

Karen R. Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER